Acyloxyphosphonium Ion Trapping

The Role of Acyloxyphosphonium Ions and the Stereochemical Influence of Base in the Phosphorane-Mediated Esterification of Alcohols**

James McNulty, Alfredo Capretta, Vladimir Laritchev, Jeff Dyck, and Al J. Robertson*

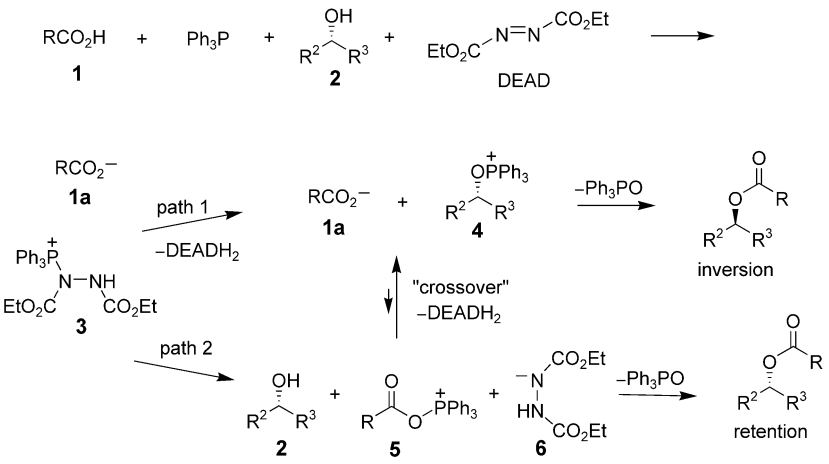
The Mitsunobu reaction[1–4] is widely employed in both condensation and displacement reactions of alcohols with various nucleophiles and normally proceeds with inversion of stereochemistry when chiral secondary alcohols are used. The mechanism of the reaction continues to receive attention and the present view is summarized in Scheme 1. Although the

[*] Dr. J. McNulty, Dr. A. Capretta, Dr. V. Laritchev
Department of Chemistry, McMaster University
1280 Main Street West, Hamilton, Ontario, L8S 4M1 (Canada)
Fax: (+1) 905-522-2509
E-mail: mcnulty@chemistry.mcmaster.ca
J. Dyck
Department of Chemistry, Brock University
St. Catharines, Ontario, L2S 3A1 (Canada)
A. J. Robertson
Cytec Canada Inc.
P.O. Box 240, Niagara Falls, Ontario, L2E 6T4 (Canada)

[**] Financial support was provided by the Natural Sciences and Engineering Research Council of Canada.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200351209



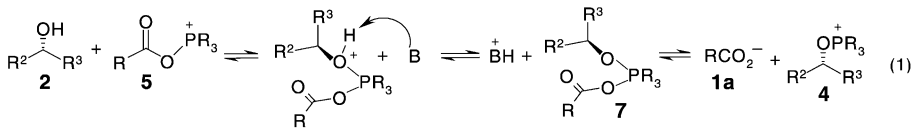
Scheme 1. Mechanism of the Mitsunobu esterification.

initiation and termination steps of the reaction seem clear cut, there is still debate concerning the exact details involved in the intermediate stages of the reaction. The reaction proceeds through the rapid addition[3a] of triphenylphosphane to an azodicarboxylate such as diethyl azodicarboxylate (DEAD), followed by proton transfer from the carboxylic acid to give **1a** and **3** as shown. As the esters obtained are the product of inversion of stereochemistry in the vast majority of cases, it appears that the reaction normally terminates through nucleophilic displacement by **1a** of triphenylphosphane oxide from the activated alkoxyphosphonium ion **4**.

Recent evidence from several laboratories has challenged the original mechanistic hypothesis put forward by Mitsunobu and Yamada,[1,2a] wherein the reaction proceeds directly to the alkoxyphosphonium salt **4** (Scheme 1, path 1). Evidence for the involvement of acyloxyphosphonium ion intermediates **5** has been obtained indirectly over a number of years.[5] Hughes et al.[3b] and Jenkins and co-workers[6] independently reported the isolation of anhydrides from the reaction of acids with DEAD and attributed this to the intermediacy of acyloxyphosphonium ions **5** that Jenkins[6] postulated were in equilibrium with **4**. More recently, DeShong and co-workers,[7] Smith et al.,[8] and De Brabander and co-workers[9] have reported the isolation of products of retention of configuration from the reactions of certain sterically hindered chiral secondary alcohols under standard Mitsunobu conditions.

Retention of stereochemistry is thought to arise through the direct attack of the alcohol at the carbonyl carbon atom of an intermediate acyloxyphosphonium salt. It has been postulated that the normal product obtained from the Mitsunobu reaction may be the result of a competitive crossover reaction mediated by basic species present or generated (such as the hydrazide anion **6**) during the reaction.[7a,10] According to this hypothesis (Scheme 1, path 2), an initial acyloxyphosphonium ion **5** is generated by the attack of the more nucleophilic carboxylate anion **1a**, rather than the alcohol, at the phosphorus center in **3**. The details of the postulated base-mediated crossover to **4** are described in Equation (1). We now report the independent generation of the benzoyloxytributylphosphonium ion, which could be trapped with chiral secondary alcohols under both neutral and basic conditions in the synthesis of esters with either retention or inversion of configuration. Clear evidence was thus obtained for both direct acylation and the postulated base-mediated crossover step.

Acyloxyphosphonium ions have been generated through the addition of a peroxide to a tertiary phosphane, for example, the addition of benzoyl peroxide (BPO) to a solution of triphenylphosphane.[11] When a solution of BPO in *N*,*N*-dimethylformamide



(1)

(DMF) was added dropwise to a mixture of L-menthol and tributylphosphane at 70 °C under argon, menthol benzoate was isolated from the reaction mixture in 50 % yield. Spectral analysis of the product showed 97 % retention of stereochemistry, which indicates that direct attack of menthol at the carbonyl carbon of the benzoyloxyphosphonium intermediate had occurred predominantly. These results concur with the postulated intermediacy of acyloxytrialkylphosphonium ions in esterification reactions, generated alternatively by using our recently described phosphorane method.[10] When this method was used, L-menthol reacted with 4-nitrobenzoic acid in DMF to give the corresponding menthol ester with 99.2 % retention of configuration (76 % yield). Recently, Burke and co-workers reported a further independent route to acyloxyphosphonium ions, from trihaloethyl esters. These species also reacted in DMF with L-menthol under nonbasic conditions to provide the corresponding esters with retention of configuration.[12]

Having demonstrated that the benzoyloxytributylphosphonium ion can be trapped with menthol to yield the desired ester with retention of configuration, we now focused on developing a more synthetically useful process that could provide access to esters with inversion of stereochemistry. We screened a large variety of bases for their ability to effect the postulated crossover step that might lead to inversion. Although essentially any amine added increased the amount of the product of inversion obtained, we quickly determined that bulky primary amines, such as *tert*-butylamine or 1,1,3,3-tetramethylbutylamine, were superior both in terms of the product of inversion/product of retention ratio observed and in terms of the yield of the desired product. The results with L-menthol show that high selectivity in favor of the product of inversion might be anticipated when such hindered bases are present (Table 1, entries 1 and 2), whereas retention of configuration is favored in the absence of a base (Table 1,

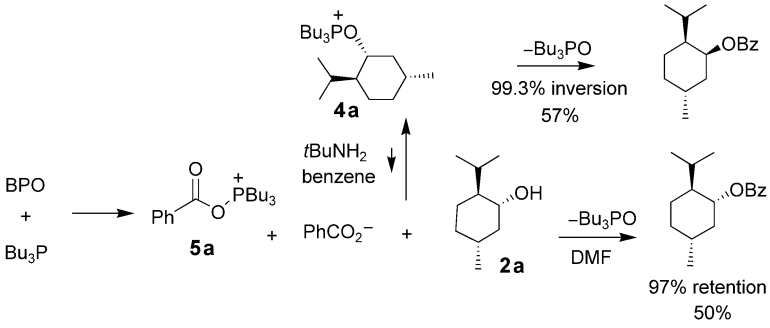
Table 1: Esterification reactions of chiral alcohols promoted by BPO/Bu_3P alone and in the presence of bulky primary amines.

Entry	Alcohol	Base	Method[a]	Ret./inv.[b]	Conv.[c]
1	L-menthol	Me_3CNH_2	A	0.7:99.3	57%
2	L-menthol	$Me_3CCH_2CMe_2NH_2$	A	1.1:98.9	55%
3	L-menthol	–	B	97.0:3.0	50%
4	(2*S*)-hexanol	$Me_3CCH_2CMe_2NH_2$	A	1.9:98.1	73%
5	(2*S*)-hexanol	–	B	55.0:45.0	67%
6	(1*R*)-1-phenyl propanol	$Me_3CCH_2CMe_2NH_2$	A	2.7:97.3	54%
7	(1*R*)-1-phenyl propanol	–	B	43.7:56.3	56%
8	ethyl (*S*)-(−)-lactate	$Me_3CCH_2CMe_2NH_2$	A	5.6:94.4	73%
9	ethyl (*S*)-(−)-lactate	–	B	72.3:27.7	70%

[a] BPO (1.5 equiv) was dissolved in 1.5 mL of benzene (protocol A) or DMF (protocol B) and added dropwise over 70 min to a stirred solution of tributylphosphane (1.5 equiv), the alcohol (1.0 equiv), and the appropriate base (2.5 equiv) in 0.5 mL of benzene or DMF at 70 °C. [b] Product of retention/product of inversion ratio determined by NMR spectroscopy and GC on a chiral phase in comparison with authentic samples. [c] Unoptimized conversion based on mass of purified ester product obtained under standard conditions described.

entry 3). These results are evidence for the base-mediated crossover step proposed in Equation (1). To the best of our knowledge, this is the first report of clear independent evidence for the involvement of a base in such a redox condensation leading to esters with inversion of configuration. These results proved to be general for the chiral secondary alcohols investigated: (2*S*)-2-hexanol (98.1% inversion), (1*R*)-1-phenyl-1-propanol (97.3% inversion), and (2*S*)-ethyl lactate (94.4% inversion).

A relatively clear mechanism can now be proposed to explain the dichotomous results obtained. In contrast with standard Mitsunobu[1] and phosphorane-mediated esterification processes,[11] in the new esterification protocol with inversion of stereochemistry in the presence of BPO/Bu_3P, direct formation of the alkoxyphosphonium ion **4a** is not possible, and the reaction must proceed via **5a** (Scheme 2).



Scheme 2. Generation and trapping of the benzoyloxytributylphosphonium ion **5a** with L-menthol.

When an alcohol is present and in the absence of base, direct acylation of the alcohol predominates, which leads to esters with retention of configuration. This process is also facilitated by the use of DMF as the solvent. In the presence of a base the crossover path becomes dominant, thus leading to the alkoxyphosphonium ion **4a**, and then to esters with inversion of configuration. The function of the base must be either to generate a continuous low concentration of alkoxide to facilitate the crossover step, or to remove a proton with formation of the phosphorane intermediate **7** [Eq. (1)], followed by dissociation to give the required alkoxyphosphonium ion **4**. In either case, the function of the base is to shift the equilibrium shown in Equation (1) to the right and promote the formation of **4**.[12]

In conclusion, we have demonstrated the independent generation of the benzoyloxytributylphosphonium ion and shown that it can be directly trapped with chiral alcohols to yield esters with retention of configuration, or can be converted into an alkoxyphosphonium ion through the addition of a base to yield esters predominantly with inversion of configuration. These studies confirm the existence of a base-induced crossover step and highlight the significance of basic species with regard to the stereochemical outcome of an esterification when such a redox condensation reaction that proceeds via an acyloxytrialkylphosphonium intermediate is used. Attention has often been drawn to the subtle interplay of factors that contribute to the stereochemical outcome in a given case.[6,7a,9,13] The results presented here show that the nature of any basic species present or generated during the reaction can have a profound effect on the stereochemistry of the esterification and thus requires due consideration.

Received: February 18, 2003 [Z51209]

Keywords: acylation · amines · peroxides · phosphanes · synthetic methods

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